REMARKS

I. RESTRICTION REQUIREMENT AND ELECTION OF SPECIES

Applicants acknowledge that Examiner has made final, despite traverse, the restriction requirement as between Group I, claims 1-33, and Group II, claims 34.

Applicants acknowledge that the Examiner has requested an election of species for search purposes only, and that Examiner has performed a search and examination with respect to claims 1-21 for at least the areas of neurodegenerative, congenital disorders and disorders resulting from exposure to teratogen.

The Examiner has withdrawn claims 22-33, relating to memory disorders on the grounds that there is, at present, no linking claim pending. As the Examiner has withdrawn claims 22-33 on the basis of an election of species for search purposes only, Applicants reserve the right, upon finding of allowability of the elected subject matter, to amend claims 22-33 so as to depend from a generic linking claim.

II. THE PENDING CLAIMS COMPLY WITH 35 USC §112, 1ST PARAGRAPH

The Examiner alleges that claims 1-21 do not comply with the enablement requirement. The Examiner argues that neither the art nor the specification provide evidence for the following features: (1) generation of a sufficient quantity of neurons; (2) differentiation of cells to neurons having desired functionality at a proper location; (3) administration at an appropriate stage of disease; (4) sustained presence of such neurons. The Examiner does not cite any art to support the assertion that these four features are necessary to establish enablement. Instead the Examiner merely states that these features are a matter of "common sense".

Applicants contend that, by requiring Applicants to produce evidence of the above-mentioned factors, the Examiner is inappropriately applying the enablement requirement. The proper legal test for enablement is generally formulated as: "[I]s the experimentation needed to practice the invention undue or unreasonable?". MPEP 2164.01, citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) and *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The pending claims are silent as to the four features the Examiner has raised, and Applicants

respectfully assert that the enablement requirement is met so long as the claimed methods may be practiced by one of ordinary skill in the art without undue experimentation.

The pending claims feature two aspects: (1) a procedure comprising the administration of bone marrow derived cells to an individual having a neuronal deficiency, and (2) ameliorating at least one symptom of the deficiency.

With respect to part (1), Applicants assert that the administration of bone marrow derived cells is common in medical practice, although it should be noted that, prior to Applicants' invention, such administration was not used for the treatment of neurological disorders lacking a known autoimmune etiology. Methods for obtaining and administering autologous and allogeneic bone marrow derived cells were well known in the art at the time of filing. For example, as noted at paragraph 004, line 2 of the present application, "bone marrow transplant (BMT) has been used extensively to rescue subjects with bone marrow failure due to myelotoxic chemotherapy/radiotherapy." While the general knowledge in the art was so extensive at the time of filing that no further discussion is necessary, the application provides further discussion of methods for obtaining, preparing and administering bone marrow derived cells. See, for example, pages 25-28.

With respect to part (2), the Examiner appears to suggest that it would require undue experimentation for one of ordinary skill in the art to ameliorate a symptom of a neurological disorder by administering bone marrow derived cells. Applicants note that this aspect of the Examiner's argument appears to be a challenge to the operability of the methods described by the Applicants. In other words, the Examiner does not suggest that one could not perform the claimed method; the Examiner appears the challenge the clinical effectiveness of the claimed methods.

Applicants respectfully maintain that no showing of treatment of a human being is required to support operability of claims directed to methods of treating disease. See, e.g., *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991). In vitro or animal based evidence that is reasonably predictive is sufficient. *Id.* Furthermore, post-filing date information may be provided to demonstrate that methods disclosed and claimed in a patent application are in fact operable. *In re Brana.*

The application as filed presents an actual reduction to practice of a method in mice, where bone marrow derived cells were administered intravascularly to mice and found to have engrafted into mouse brains and to have given rise to neuronal cell types. These data were published in the scientific literature and the findings have been confirmed or extended by many others. See, for example, Hess et al. (Stroke 2002 33:1362-8), Reference AT.

After the filing date of the present application, the methods disclosed and claimed have been used successfully to achieve symptomatic improvements in animal models for various human neurological disorders. Under In re Brana, such post-filing date evidence is acceptable to establish the operability of methods taught in the present application at the time of filing.

A Declaration under 37 C.F.R. §1.132 is attached hereto. This declaration was prepared with Dr. Timothy Brazelton, one of the named inventors of the present application. The declaration is provided here in unexecuted format. The executed document will be filed shortly. The declaration describes experiments using the intravascular administration of bone marrow cells to alleviate Parkinsonian symptoms in a well-respected mouse model for Parkinson's disease. As noted in the Declaration, the chemical MPTP induces similar Parkinsonian symptoms in both humans and mice. Thus it is generally expected that a treatment regimen that ameliorates such symptoms in a mouse model is reasonably likely to have a similar effect in humans. Figures 1 and 2 presented in Exhibit BB show that the administration of bone marrow derived cells to the MPTP treated mice causes a substantial improvement in Parkinsonian symptoms. The information provided in the Declaration demonstrates that the methodology described in the present application at the time of filing can be practiced successfully to ameliorate the symptoms of a neurodegenerative disorder, such as Parkinson's disease.

Additionally, other scientists in the field have used methods described in the present application to achieve beneficial results in rodent models for stroke. Chen et al. (Reference AR, Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, Chopp M. Stroke 2001 Apr;32(4):1005-11) administered bone marrow derived cells to rats having neurological damage resulting from induced events that closely resemble stroke in humans. Chen et al. administered cells intravenously and achieved significant improvement in recovery of neurological functions. While Chen et al. did not design their experiments to allow post-treatment identification of transplanted cells in the brain, Hess et al. (Reference AT; Hess DC, Hill WD, Martin-Studdard

A, Carroll J, Brailer J, Carothers J. Stroke 2002 May;33(5):1362-8) used histological methods to confirm that bone marrow derived cells administered to an animal model for stroke contribute to the neuronal cell population in the affected brains. Six et al. (Reference AS; Six I, Gasan G, Mura E, Bordet R. Eur J Pharmacol. 2003 Jan 5;458(3):327-8) took an approach that is virtually identical to that claimed in non-elected claim 34, using mobilizing factors to increase the mobilization of bone marrow derived cells into the bloodstream of an animal model for stroke. This approach also facilitated the recovery of neurological function. Applicants concede that the mobilization method is not presently under examination, however, the data do tend to confirm the significance and operability of the general principles described in the present application.

Taken together, the data presented in the Declaration, and the data of Chen et al., Hess et al., and Six et al., demonstrate that bone marrow derived cells can in fact be administered to a mammal suffering from a neurological disorder, including a neurodegenerative disorder, and successfully ameliorate one or more clinical symproms.

Accordingly, Applicants assert that the specification fully enables one of ordinary skill in the art to administer bone marrow derived cells to an individual suffering from a neurological disorder so as to ameliorate one or more symptoms.

In formulating the rejection, the Examiner has cited a variety of art in an effort to establish nonenablement of the pending claims. Applicants do not believe that the cited art is relevant to the claims at hand.

Burt et al. (Blood 1998 91:2609-16) describes experiments designed to test whether bone marrow transplantation would reduce glial scarring in a mouse model for a neurological autoimmune disease. In other words, Burt et al. only looked to whether the new bone marrow cells would have a decreased tendency to produce immune cells that attack self antigens. Burt et al. did not evaluate any possible generation of neurons from the bone marrow transplant and Burt et al. provides no indication of the likely success of the claimed procedure in a non-autoimmune disorder.

Donovan and Gearhart (Nature 2001 414:92-97) is addressed solely to problems in the area of embryonic stem cell transplants. Embryonic stem cells pose very different challenges

from bone marrow derived stem cells and are not relevant to a discussion of bone marrow derived stem cells.

Sugaya (CMLS 2003 60:1891-1902), Galvin (MJA 2002 177:316-18) and Weissman (Science 2000 287:1442-46) are all directed to difficulties in moving from animals to humans. But note that the case law, cited above, does not require all difficulties in humans to have been addressed in order to adequately establish the operability of inventions directed to therapeutics and methods of treatment. Applicants note that Sugaya does not, contrary to Examiner's statement, explicitly mention bone marrow derived stem cells, and therefore the relevance of this reference is questionable.

The Examiner has also cited Sugaya et al. for the proposition that mild damage to the nervous system prior to or concomitantly with administering cells will not predictably facilitate treatment. Applicants assert that it is a matter of routine experimentation for one of skill in the art to assess the appropriate level of damage to employ. It has been observed that the creation of damage in the CNS increases the production of several neurotrophic factors and can enhance the engraftment of transplanted cell (Reference AV; Nieto-Sampedro et al, J Neurosci 1983 3:2219-29).

The Examiner has cited Game et al. as indicating that rejection will be problematic for allogeneic and xenogeneic transplants. Applicants note that similar rejection problems are faced by surgeons performing solid organ transplants. Nonetheless, a variety of immunosuppressants have been employed with sufficient success to allow organ transplantation. Admittedly, such transplantation protocols are generally reserved for diseases that cannot be successfully treated in any other way. However, Applicants note that the neurological disorders that may be treated by the present methods are, for the most part, presently untreatable and debilitating. The risks associated with immunosuppressive therapy are likely to be acceptable in these populations. Applicants further note that safety testing and an absence of side effects is not required for patentability. The patent examination process is not a substitute for regulatory approval of a therapeutic regimen, and the criteria are not the same.

Applicants respectfully request reconsideration and withdrawal of the rejections of the pending claims for alleged lack of enablement.

II. THE CLAIMED SUBJECT MATTER IS NOT ANTICIPATED OR RENDERED OBVIOUS BY THE ART

U.S. Patent Publication No. 2002/0146821 to Sanchez-Ramos et al. (the '821 publication)

The Examiner has rejected claims 1-10 and 13-21 as anticipated by the '821 publication under 35 U.S.C. § 102(e). The Examiner has also rejected claims 1, 8, and 10-12 as unpatentable over the '821 publication in view of Weiss et al. U.S. Patent No. 6,071,889.

The Examiner argues that the '821 publication teaches "a method for treating a neuronal deficiency comprising administering bone marrow-derived cells to an individual having a neurodegenerative disorder such as Parkinson's disease (implicating such use in a human subject, paragraph 0039)...." The Examiner further argues that Weiss et al. supplement the teachings of the '821 publication so as to render obvious claims directed to the separate administration of cells and a growth factor.

Applicants respectfully disagree with this rejection on the grounds that the '821 publication does not provide an enabling disclosure for the use of bone marrow derived cells in the treatment of neurological disorders. Furthermore, the deficiencies of the '821 publication are not cured by the Weiss et al. patent. While Applicants believe it to be unnecessary at this time, Applicants reserve the right to file a Declaration pursuant to 37 CFR 1.131 to demonstrate invention prior to the earliest valid priority date of the '821 publication.

Applicants note that the teachings of the '821 publication are restricted to the use of bone marrow stromal cells that have been cultured in the presence of retinoic acid in vitro prior to administration directly to the CNS. While Applicants do not, at this time, challenge the veracity of the in vitro cell culture data presented in the '821 publication, Applicants wish to draw the Examiner's attention to a publication by the inventors listed on the '821 publication. In this publication, Sanchez-Ramos et al. (Reference AU) disclaim the very same in vivo data that is presented in example 3 of the '821 publication.

Sanchez-Ramos et al. explain that beta-galactosidase is an unreliable and difficult marker to use in neurological cell transplant experiments. Neuronal cells tend to express high levels of endogenous beta-galactosidase, meaning that it is difficult to differentiate transplanted and

endogenous cell types. Beginning at page 658, Sanchez-Ramos describe the beta-galactosidase approach as a "booby trap", and they describe in detail the very experiments and data that are presented in example 3 of the '821 publication. At page 660, Sanchez-Ramos et al. write, "At first blush, these results suggested the astounding result that *lacZ*-expressing, donor-derived, BMSC's had migrated extensively and had differentiated into neural cells in a site-dependent manner. However...we were observing factitious X-gal staining that was leading to the misidentification of endogenous cells as donor-derived cells."

Therefore, the inventors of the '821 publication have themselves rejected their own data showing the in vivo capability of bone marrow derived cells to become neurons. Sanchez-Ramos et al. also refer to the discovery presented in the instant application as a result that would be "astounding". Accordingly, one of ordinary skill in the art would not read the '821 publication and the accompanying Sanchez-Ramos reference as suggesting that bone marrow derived cells can, in vivo, maintain neuronal fates that would be useful in treating a neurological disorder.

Applicants note that the Examiner has failed to cite any post-filing date evidence (or other evidence) to suggest that the procedures taught in the '821 publication have ever proven useful in any mouse model for a neurological disorder. It is not reasonable to suppose that one of ordinary skill in the art could practice the teachings of the '821 publication without undue experimentation.

Applicants respectfully request reconsideration of all rejections under 35 U.S.C. § 102(e) and 103(a) in view of the '821 publication.